

Room Temperature Palladium-Catalysed Coupling of Amino Acid-Derived Organozinc Reagents with Aryl Triflates

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Abstract—Aryl triflates may be cross-coupled with the amino acid derived zinc reagents 1, 2 and 3 using palladium catalysis at room temperature, in the presence of anhydrous lithium chloride, conveniently yielding phenylalanine 4, β -homophenylalanine 5 and γ -bishomophenylalanine 6 derivatives respectively (nine examples). © 2000 Elsevier Science Ltd. All rights reserved.

Our previous synthetic approach to substituted phenylalanines, β -homophenylalanines and γ -bishomophenylalanines relied on coupling of zinc reagents with aryl iodides.^{1,2} Given the easier access (in general)³ to aryl triflates, we have explored the coupling of the zinc reagents **1**, **2** and **3** with aryl triflates. Palladium catalysed coupling of aryl (and heteroaryl) triflates with alkyl,^{4,5} benzylic^{6,7} and aryl^{8–10} zinc reagents has been reported, as well as a recent example using zinc cyanide.¹¹ Lipshutz has also recently described a nickel catalysed cross-coupling reaction of an organozinc reagent with a naphthyl triflate.¹² Several cost effective alternatives to triflates; vinyl nonaflates¹³ and aryl fluorosulfonates¹⁴ have been examined in the context of crosscoupling reactions with organozincs.



Results and Discussion

Simply replacing iodobenzene with phenyl triflate under our optimum conditions for aryl iodide coupling with the aspar-

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tic acid derived zinc reagent 2 failed to furnish any coupled product, in contrast to the good yield of 5a (73%) obtained when using iodobenzene as the electrophile. In general, the literature examples referred to above required heating in order to obtain high yields. These conditions are unsuitable for the functionalised zinc reagents 2 and 3, which undergo rapid β -elimination. However, after extensive screening of a variety of catalysts, ligands and additives, a combination which did not require elevated temperature was identified, but which had previously been employed at elevated temperature.⁴ Room temperature coupling of zinc reagent 2 with phenyl triflate, in the presence of three equivalents of rigorously dried lithium chloride, resulted in an acceptable vield (58%) of coupled product 5a. Using these optimum conditions, cross-coupling reactions were carried out between zinc reagents 1, 2 and 3 and phenyl, naphthyl and *p*-nitrophenyl triflates to furnish the coupled products shown below (Scheme 1 and Table 1).

The yields of reaction are typically all lower than when the corresponding aryl iodides are used as electrophiles, but the scope of the process has been extended significantly. The role of the lithium chloride is presumably to act as source of chloride ions to stabilise the palladium catalyst, in a manner analogous to that postulated by Stille in the cross-coupling of alkylstannanes with aryl triflates.¹⁵ Interestingly, the yields of coupled product obtained with the serine derived zinc reagent 1 are significantly lower than when homologous zinc reagents 2 and 3 are coupled with any triflates. This may be a reflection of the internal coordination observed between the ester and zinc,² making this zinc species a bulkier nucleophile, even in DMF. Alternatively, the lower yields may be simply due to the electron withdrawing ester group being closer to the metal bearing carbon.

Keywords: amino acids; palladium; cross-coupling; zinc.

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Scheme 1.

Table 1. Yields of products from the palladium(0) catalysed cross-coupling reaction of aryl triflates with zinc reagents 1, 2 and 3

Ar	Zinc reagent	Coupled product	% Yield ^a
C ₆ H ₅	1	4a	7
C ₆ H ₅	2	5a	58
C ₆ H ₅	3	6a	44
1-Naphth	1	4b	39
1-Naphth	2	5b	64
1-Naphth	3	6b	49
p-NO ₂ -C ₆ H ₄	1	4c	30
$p-NO_2-C_6H_4$	2	5c	44
p-NO ₂ -C ₆ H ₄	3	6с	29

^a Yields are based on amino acid derived iodide precursors (0.75 mmol).

It appeared from analysis of the crude NMR spectra, especially in the case of the *p*-nitrophenyl triflate, that a significant proportion of the corresponding biaryl product was present. This probably arises from the presence of a small amount of residual zinc which is present after formation of the zinc reagents. Jutand has previously commented on the scope of forming symmetrical biaryls from the palladium catalysed homocoupling of aryl triflates in the presence of zinc dust.¹⁶

Experimental

Zinc dust (0.294 g, 4.5 mmol, 6.0 equiv.) was weighed into a 50 mL round bottom flask with side arm which was flushed with nitrogen. Dry DMF (0.5 mL) and 1,2-dibromoethane (19 µL, 0.225 mmol) were added and the mixture was stirred vigorously. The mixture was heated on a hot water bath for 20 min before being allowed to attain ambient temperature. Trimethylsilyl chloride (6 µL, 0.046 mmol) was added to the mixture, which was stirred for a further 30 min. The appropriate alkyl iodide precursor to zinc reagents $\mathbf{1}^{1}, \mathbf{2}$ or $\mathbf{3}^{2}$ (0.75 mmol) was dissolved in dry DMF (0.5 mL) under nitrogen. The iodide solution was transferred by syringe to the zinc mixture and stirred at room temperature. TLC (petroleum ether-ethyl acetate, 2:1) showed complete consumption of starting material within 15 min. At this stage the electrophile (1.0 mmol) was added together with Pd₂(dba)₃ (0.023 g, 0.025 mmol), (o-tol)₃P (0.030 g, 0.10 mmol) and LiCl (0.127 g, 3.0 mmol). The mixture was allowed to stir at room temperature for 3 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and saturated aqueous ammonium chloride (20 mL) then filtered. The organic layer was washed with water (20 mL) and brine (20 mL), then dried and the solvent removed under reduced pressure. Flash column chromatography yielded protected aryl amino acids which exhibited spectroscopic characteristics identical to the compounds prepared previously using aryl iodides as electrophiles, and which we have already reported. For compounds **4a**-**c** see Ref. 1 and for compounds **5a**-**c** and **6a**-**c** see Ref. 2.

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